in the specification, and the quantity of experimentation necessary would clearly require undue experimentation to determine how to use the claimed method of inhibiting phenotypic expression of a chemokine receptor in a cell *in vivo*, or the claimed method of inhibited HIV infection of a cell *in vivo*. Applicants traverse this rejection.

A specification that contains a disclosure of how to make and use the invention that is commensurate with the scope of the claims must be taken as sufficient to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason that one of skill in the art would question the objective truth of the disclosure. Thus, a statement of enablement must be presumed to be true:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. (emphasis added).

In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

The Examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *Wertheim,* 541 F.2d at 263, 191 USPQ at 97.

There is no requirement under the current law of enablement that each embodiment be reduced to practice. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991). "[I]f any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention." MPEP 2164.01(c). The only disease recited in the claims is HIV. The only *in vivo* method recited in the claims is a method to increase the white blood cell count in an individual with HIV infection using an *ex vivo* approach. The specification discloses that one use of the expression vectors and methods of the invention is in *ex vivo* gene therapy (specification, page 5, lines 1-19, among other places).

It is improper for the Examiner to require that claimed invention be enabled for the entire field of gene therapy and for every disease mentioned in the specification. Only one use for the expression vectors and methods of the invention is required by law.

The Examiner characterizes the utility of the vectors and methods of the invention as requiring the delivery of a nucleic acid through *in vivo* and *ex vivo* gene therapy techniques, yet improperly directs the substance of the rejection to the *in vivo* gene therapy techniques and does not specifically address the *ex vivo* gene therapy techniques. The utility of the vectors and methods of the invention is disclosed to include *ex vivo* gene therapy techniques which do not have many of the drawbacks of *in vivo* gene therapy techniques (see arguments that follow), and use lymphocyte cell transplantation, which is acknowledged to be well established in the Verma reference.

The Examiner uses Verma to assert a "complete lack of success with any treatment based on gene therapy" (Office Action of July 17, 2001, page 5, line 14). Clinical trials are not the only way in which a technique can be shown to be successful, experimental results are also useful. Verma is cited for the proposition that gene therapy is problematic because of host immune responses against the viral vector (citing Verma p 239, col. 3, third paragraph); however, this statement is made in the context of *in vivo* gene therapy, and does not address *ex vivo* gene therapy. *Ex vivo* gene therapy transforms the cells outside the patient's body, and then introduces the transformed cells into the patient. Therefore, in *ex vivo* gene therapy, the viral vector is not exposed to the immune system directly. The aspect of poor transformation efficiency pointed out by the Examiner (citing Verma, page 239, col. 3, paragraph 2) is again in the context of *in vivo* gene therapy: the same paragraph of Verma refers to "direct injection of DNA" which then crosses the cell membrane (Verma, page 239, col. 3, paragraph 2, lines 8-11). Verma states that "[o]ur view is that, in the not too distant future, gene therapy will become routine a practice as heart transplants are today" Verma, page 242, col. 3, paragraph 3, emphasis added). In light that the publication date of Verma is two years before the filing date of the present application, Verma is optimistic that gene therapy will not entail undue experimentation at the time the application was filed.

Verma and others report success with *ex vivo* gene therapy. Anderson et al. (U.S. Patent No. 5,399,346, issued March 21, 1995) reports success with hADA transduced T-

lymphocytes (See Example 5 and Figure 5, among other places). Verma reports success in the context of transforming primary fibroblasts and myoblasts and introducing them into mice. Problems with gene shut off (Verma page 240, col. 2, line 12) and inefficient fusion of cells to body tissue (Verma, page 230, col. 3, paragraph 2) do not invalidate the enablement of the present invention where recurrent administration of transformed cells is contemplated (specification, page 5, line 17, among other places). Further, Verma is very optimistic about the use of the hematopoietic system for *ex vivo* gene therapy:

> The haematopoietic (blood-producing) system may offer an advantage for ex vivo gene therapy because resting stem cells can be stimulated to divide in vitro using growth factors and the transplantation technology is well established." (Verma, page 240, col. 3, para. 2).

Therefore, one of skill in the art, upon reading Verma at the time of filing, would not doubt that gene therapy, and in particular *ex vivo* gene therapy, was possible without undue experimentation.

The Examiner cites Fox (ASM News, Feb. 2000 66(2):1-3) as evidence that the area of the invention is unpredictable. The Fox article states that the University of Pennsylvania clinical trial was only one among "several hundred gene transfer and gene therapy clinical procedures now under way." In light of the magnitude of clinical trials being done, the fact that this one unfortunate death made the national news suggests the overall safe and predictable nature of the procedure. The fact that many gene therapy procedures have entered clinical trials further indicates that the scientific community considers these procedures to hold great promise of success. Further, the University of Pennsylvania study that is the subject of Fox was an *in vivo* gene therapy technique involving the administration of a genetically engineered adeno-virus vector directly to patients (Fox, page 2, paragraph 5), and does not speak to *ex vivo* gene therapy techniques. One of skill in the art, upon reading Fox, would not doubt that gene therapy techniques, and in particular *ex vivo* gene therapy techniques, could be performed without undue experimentation.

The Examiner alleges that the specification provided insufficient guidance to support the claimed invention for gene therapy applications. Support for the success of the invention in patients is indicated, among other things, by the well-known observation that HIV patients with a heterologous CCR5 defect exhibit slower progression of the disease, and

patients whose lymphocytes express high levels of CC-chemokines are partially resistant to HIV-1 infection (specification, page 1, lines 23-29 and the references cited therein). In light of the success in making lymphocytes expressing intracellular CXC-chemokines which are resistant to HIV-1 infection in vitro and the well-known reports of the phenotypes of HIV-1 resistant individuals and the well-established nature of lymphocyte transplantation technology (Verma, page 240, col. 3, para. 2), one of skill in the art would not doubt that the vectors and methods of the invention would be helpful in treating patients with HIV-1.

The application contains a working example of *ex vivo* gene therapy by incorporation of U.S. Patent Application 5,399,346 (Anderson et al., issued March 21, 1995), and attention is directed to the sections which disclose *ex vivo* therapeutic methods (specification, page 34, lines 1-2). An application as filed must be complete in itself in order to comply with 35 U.S.C. 112. Material nevertheless may be incorporated by reference. *Ex parte Schwarze*, 151 USPQ 426 (Bd. App. 1966). A copy of U.S. Patent No. 5,399,346 was included in the Information Disclosure Statement, filed May 11, 2000, in the present application. The Anderson Patent discloses many details of the technique of *ex vivo* gene therapy, including success using *ex vivo* gene therapy with lymphocytes in which a defective ADA gene is replaced (see, in particular, Example 5 and claim 4). This successful working example, would lead one of skill in the art to believe, rather that doubt, that they could made and use the claimed invention of the present application.

In summary, the Examiner asserts that quantity of experiment is high with regard to several steps of the invention due to lack of teachings in the specification and the prior art (Office Action of July 17, 2001, page 7, paragraph 3). The Examiner concedes that the specification and/or prior art disclose cell surface receptors and associated ligands for HIV (Office Action of April 23, 2002, page 7, lines 6-8). The effect of exogenous transgene expression is disclosed when SDF is expressed in lymphocytes where it prevents the transport of the CXR4 receptor to the cell surface (specification, page 43, among other places). It is disclosed that the lymphocytes with the phenotypic CXR4 knockout were resistant to T-tropic HIV-1 infection (specification, page 43, line 29 and following). It is disclosed how to transform mammalian cells, including lymphocytes, *in vitro* with specificity and efficiency (specification, page 31, line 20 and following), and to introduce these transformed cells,

particularly lymphocytes, into a patient for the purposes of gene therapy (specification, page 33, line 29 to page 34, line 5; page 36, line 13 to page 37, line 25); and throughout the specification; U.S. Patent No. 5,399,346, throughout). It is disclosed how to get sufficient gene expression to obtain a therapeutic effect against HIV-1 (specification, Example 5). In light of this specific disclosure, one of skill would not doubt that they could make and use the invention to increase the white blood cell of an individual with an AIDS infection.

Applicants request that the rejection of claims 1-24, 29, and 33-39 pursuant to 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Rejection of claim 19 pursuant to 35 U.S.C. § 112, first paragraph

Claim 19 stands rejected under 35 U.S.C. § 112, first paragraph, because in the view of the Examiner, it contains subject matter that is not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventors, at the time that application was filed, had possession of the claimed invention. Specifically, the Examiner asserts that the specification does not provide sufficient description of "chemokine analog."

While not conceding to the validity of this rejection, Applicants have amended the claim 19. This amendment is undertaken in order to promote the issuance of commercially valuable claims. Applicants reserve the right to pursue any scope lost due to this amendment in continuing applications. Claim 19 has been amended to recite "the chemokine analog RANTES(9-68)". Support for this amendment is found in the specification (page 3, lines 13-15), and no new matter is added. The RANTES(9-68) chemokine analog is disclosed in the Arenzana-Seisdedos reference, which was incorporated by reference and included among the IDS references.

Applicants request that the rejection of claim 19 pursuant to 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Rejection of claims 1-16, 18-22, 29 and 33-39 pursuant to 35 U.S.C. § 112, first paragraph

Claims 1-16, 18-22, 29 and 33-39 stand rejected under 35 U.S.C. § 112, first paragraph, because in the view of the Examiner, they contain subject matter that is not described in the specification in such a way as to reasonably convey to one of skill in the art

that the inventors, at the time that application was filed, had possession of the claimed invention.

Specifically, the Examiner objects to the use of the terms "chemokine encoding gene," "chemokine receptor binding polypeptide gene" and "CC-chemokine gene." The Examiner asserts that a representative number of eukaryotic genes for receptor binding polypeptides or chemokines is not known. The Examiner states that this rejection would be overcome by amending the claims to recite "coding region" (Office Action of April 23, 2002, page 11, lines 3-4).

While not conceding to the validity of this rejection, Applicants as amended the claims according the Examiner suggestion. This amendment is undertaken in order to promote the issuance of commercially valuable claims, and Applicants reserve the right to pursue any scope lost due to this amendment in continuing applications. Claim 1 has been amended to recite "chemokine encoding region." Claim 18 has been amended to recite "chemokine receptor binding polypeptide coding region." Claim 29 has been amended to recite "CC-chemokine coding region." Claim 35 has been amended to recite "chemokine encoding region." Support for these amendments is found in the specification (page 11, lines 29-30). These amendments introduce no new matter.

Applicants request that the rejection of claims 1-16, 18-22, 29 and 33-39 pursuant to § 112, first paragraph, be reconsidered and withdrawn.

Rejection of claims 1-16 pursuant to 35 U.S.C. § 112, second paragraph

Claims 1-16 stand rejected under 35 U.S.C. § 112, second paragraph, because in the view of the Examiner, they are indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Specifically, the Examiner asserts that the phrase "the expression region" in line 1 of claim 1 has insufficient antecedent basis.

Claim 1 has been amended to recite "An expression vector which comprises an expression region." Support for this amendment is found in claim 1 as filed, as it would be clear to one of skill in art that "an expression vector wherein the expression region" defines the expression vector as having an expression region. This amendment introduces no new

matter. Applicants assert that this amendment gives "the expression region" antecedent basis, removing this ground for rejection.

Applicants request that the rejection of claims 1-16 pursuant to §112, second paragraph, be reconsidered and withdrawn.

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been overcome or is now inapplicable, and that each of currently pending claims 1-24, 29, and 33-39 is in condition for allowance. Reconsideration and allowance of claims 1-24, 29, and 33-39 are respectfully requested at the earliest possible date.

Respectfully submitted,

CHEN *ET AL.*

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(Date)

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Enclosures (petition for three-month extension of time and fee therefor; notice of change of address; "marked-up" copy of the claims)

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Marked-Up Copy of the Claims

1. An expression vector which comprises an expression region, wherein the expression region comprises:

a promoter;

an intracellular retention signal sequence encoding region; and a

chemokine encoding [gene] region;

wherein said intracellular retention signal sequence and said chemokine encoding [gene] region are expressed from said promoter as a single intrakine transcript.

18. The method of claim 17, further defined as comprising the steps of:

obtaining a vector comprising a nucleic acid segment encoding a promoter; an intracellular retention signal sequence and a chemokine receptor binding polypeptide gene; and

transducing said vector into said cell;

wherein said vector expresses said intracellular retention signal sequence and chemokine receptor binding polypeptide [gene] coding region under the transcriptional control of said promoter to produce a fusion polypeptide when transduced into said cell.

19. The method of claim 18, wherein said polypeptide is a chemokine, [a] the chemokine analog RANTES(9-68), an antibody or a peptide.

29. The method of claim 24, wherein said cell is transduced with a CC-chemokine [gene] coding region fused to an endoplasmic reticulum (ER)-retention signal to intracellularly block the transport and surface expression of an endogenous CC receptor.

35. (Amended) An expression vector for treatment of an HIV infection in a subject, wherein said expression vector includes:

an expression region which comprises:

a promoter;

an intracellular retention signal sequence encoding region; and

a chemokine encoding [gene] region;

wherein said intracellular retention signal sequence and said chemokine encoding [gene] region are expressed as a single intrakine transcript from said promoter; and

wherein when said expression vector is administered to lymphocytes, monocytes, macrophages or stem cells of said subject said cells exhibit a phenotypic knock out of an HIV co-receptor.

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